Remarks

Reconsideration is respectfully requested.

Entry of the amendments is believed proper as submission of this amendment and reply is accompanied by the filing of a Request for Continued Examination. Upon entry of the foregoing amendment, claims 55-68, 71-81, 83, 84, 106-111, 113, 114, 130, 134-149 are pending in the application, with claim 55, 56, 71, 72, 106, 113 and 136 being the independent claims. Claim 149 is new. Claims 72-81, 83, 84, 106-111, 136, 137 and 141 are withdrawn. Active pending claims 55, 56, 63, 66, 68, 71, 113 and 114 are sought to be amended. Withdrawn claims 72-74, 83, 106, 109, 136 and 137 are sought to be amended. Claims 69, 70, 82, 131-133 have been cancelled from the latest pending claim set.

Claim 149 is new. Claims 149 reads, *inter alia*, on the elected, active group and on certain withdrawn groups. Support for new claim 149 is found, *inter alia,*, at specification paragraphs [0038], [0186] and [0196], and in Figure 6 (initiator is 1 nucleotide), Figure 17 (initiator is two nucleotides) and Figure 19 (initiator is 3 nucleotides).

Support for amending the preamble of claim 55 to refer to a "single-stranded" DNA or RNA "target polynucleotide" is found, *inter alia*, at specification page 9, paragraph [0022].

Support for the amendments concerning the hybridization of a target polynucleotide with a target specific linker of an abortive promoter cassette and the abortive promoter cassette itself in part (a) of claims 55, 56, 72, 136, in part (c) of claim 71 and in part (b) of claim 113 is found, e.g., in Figures 19 and 20, at specification pages 55 and 56, paragraphs [0151] and [0152], and throughout the specification as filed.

Support for the amendments concerning the incubation of said "hybridized" target polynucleotide "and linker of part (a/c/b)" in part (b) of claims 55, 56, 72, 136, in part (d) of claim 71 and in part (c) of claim 113 is found, e.g., in Figures 19 and 20, and throughout the specification as filed.

Support for the amendment concerning the synthesis process of an oligonucleotide transcript, namely "said process does not use said single-stranded target polynucleotide as a template", in part (c) of claims 55, 56, 72, 136, in part (e) of claim 71 and in part (d) of claim 113 is found, e.g., in Figures 19 and 20, and throughout the specification as filed.

Currently amended claims 63 and 68 have been reformulated to clarify the lengths of the abortive oligonucleotides and the initiators, respectively. Support can *inter alia* be found in previously pending claims 63 and 68.

Support for amended claim 66 can *inter alia* be found in parent claim 56.

Support for the amendment "in a different region than the hybridization region of a target specific linker of an abortive promoter cassette" in part (a) of claim 73, in claim

114 and in part (b) of claim 137 is found, e.g., in Figures 19, 20 and 21, and throughout the specification as filed.

Support for the amendment in claim 74 concerning the detection and quantification of said reiteratively synthesized oligonucleotide is found *inter alia* at specification pages 87 and 88, paragraph [0214].

Support for amended claim 83 can *inter alia* be found in parent claim 72.

Support for amended claim 106 is found *inter alia* on specification page 92, paragraphs [0225] and [0226] and Figure 22. Concerning the abortive promoter cassettes of part (a) of claim 106, support is *inter alia* found at specification pages 55 and 56, paragraphs [0151] and [0152].

Support for amended claim 109 can *inter alia* be found in parent claim 106.

No new matter has been added by these amendments.

Based on the amendments and the following remarks, Applicant respectfully requests that the Examiner reconsider all outstanding rejections and that they be withdrawn.

Statement of the Substance of the Interview

Applicant sincerely thanks Examiner Kim for the courteous and helpful interview granted to Applicant's undersigned attorney on November 25, 2008. At the interview

Applicant was granted the opportunity to discuss the invention, the outstanding rejections and the amendments to the claims.

Applicant was also granted the opportunity to discuss the possibility of rejoinder of non-elected groups. Applicant sincerely thanks Examiner Kim for stating that he will consider rejoining the groups. Applicant's discussion in that regard is presented below in greater detail.

Applicant has not yet received the interview summary by the time this statement is being filed. Applicant requests that, if possible, if the Examiner's interview summary has not yet been completed, that it indicate that in light of Applicant's comments in this amendment and reply, that no further statement of the substance of the interview is necessary.

Request for Rejoinder if the Claims of Group I are Allowed

Applicant has amended the withdrawn claims for Groups II through IV, in a manner similar to the amendments to the claims of active Group I (but with broader aspect for withdrawn Group III as described below), and respectfully request rejoinder if the claims of group I are allowed.

As discussed at the interview, withdrawn claims for Group II (claims 72-81 and claims 83, 84) are directed to a method of detecting mRNA. Applicant respectfully submits that mRNA represents a sub-population of the RNA embodiments of elected Group I. Thus, in Applicant's opinion, claims for Group II are clearly linked to claims of

Group I, and having been amended herewith in a manner similar to Group I, can, and should, be rejoined.

As discussed at the interview, withdrawn claims for Group III (claims 106-111) are directed to a method of detecting a target protein in a test sample. Applicant respectfully submits that the identical readout system for an interaction as in Group I is used, namely oligonucleotide transcripts synthesized using an abortive promoter cassette. Said readout system comprises an abortive promoter cassette of allowed claim 1 of the meanwhile allowed Application No. 10/790,766 wherein the target-specific linker is not a nucleic acid (see discussion below for details). Applicant respectfully submits that claims for Group I and Group III differ in said target-specific linker only whereas the basic principle and thus the inventive concept of the detection method is identical.

As discussed at the interview, withdrawn claims for Group IV (claims 136, 137 and 141) are directed to a method of detecting a single-stranded DNA or RNA target polynucleotide in a test sample. Applicant respectfully submits that the method of Group IV differs from the method of Group I only in that no terminator is added to said hybridized target polynucleotide and linker of part (a) in step (b). However, an initiator and RNA-polymerase are added. And, although the presence or absence of a terminator formed a basis for the restriction requirement in this application, Applicant respectfully submits that the presence or absence of a terminator does not represent the inventive concept since the synthesis reaction will produce oligonucleotide transcripts using a sequence of the abortive promoter cassette (and not of the target polynucleotide) as template.

Thus, the synthesis reaction will be terminated whenever the amplification of said template has been finished and then start again. By choosing e.g. a relatively short template sequence within the abortive promoter cassette, reiterative short oligonucleotides will be produced and serve as readout of the interaction reaction.

Applicant respectfully submits that claims for Group I and for Group IV are thus directed towards the same inventive concept, and can be properly rejoined.

Rejection under 35 U.S.C. § 103

The First 103 Rejection

The Examiner rejected claims 55-70, 113, 130, 133-135, 138-140, 142-148 under 35 U.S.C. § 103(a) as allegedly unpatentable over Dattagupta (U.S. Pat. No. 5,215,899) in view of Sasaki *et al.*

The Examiner contended that Dattagupta discloses, *inter alia*, hybridization of an abortive promoter cassette with a single stranded target polynucleotide and that while Dattagupta does not disclose the incorporation of a terminator in the reaction, such would be obvious in view of the teachings of Sasaki *et al.* The Examiner contended that Sasaki *et al.* discloses a transcriptional sequencing method comprising, *inter alia*, hybridizing a single stranded target polynucleotide with an abortive promoter cassette comprising a sequence that hybridizes to the single stranded target polynucleotide, and a region that can be detected by transcription by a polymerase. The Examiner contended that Sasaki *et al.* discloses incubating the target polynucleotide with an RNA

polymerase, an initiator, and a terminator and detecting the oligonucleotide transcripts by electrophoresis sequencing method.

The Examiner contended that while Sasaki *et al.* involve a different method for transcriptional sequencing, one of ordinary skill in the art would have clearly recognized that the method provided for by Dattagupta would also have been capable of conducting transcriptional sequencing by incorporating nucleotide chain terminators in their reaction. The Examiner further contended that one of ordinary skill in the art would have had a reasonable expectation of success at combining the teachings since both methods involve generation of nucleic acid constructs comprising promoter sequences.

The Examiner did not find the Applicant's arguments persuasive as put forward in the Amendment received on June 11, 2008. Thus, the Examiner did not accept the argument that Sasaki *et al.* is directed to a different method, namely transcriptional sequencing, since the basis for the nonobviousness objection is, in the Examiner's opinion, a combination of the two references, namely Dattagupta and Sasaki *et al.* The Examiner contended that the term "abortive, reiterative process" does still encompass embodiments wherein a plurality of transcripts of very different sizes is generated, as, e.g., in transcriptional sequencing methods. Finally the Examiner traversed the Applicant's argument that detection has not been employed in the prior art by stating that "sequencing" should be considered to be under the confines of "detection".

Applicant respectfully traverses this rejection and respectfully request reconsideration. Applicant, respectfully, disagrees with the Examiner's analysis of the cited art.

Applicant's claims are neither directed to methods of detecting a nucleic acid using amplification of the sequence that is to be detected as discussed by Dattagupta nor to transcriptional sequencing methods using amplification (in an abortive way) of the sequence that is to be sequenced as discussed by Sasaki *et al.* Applicant's claims are directed to methods of detecting DNA or RNA in test samples using a mechanism, which combines two mechanisms, namely a detection mechanism by hybridization to a polynucleotide that is to be detected and, as a readout for said detection step, an amplification mechanism using an abortive amplification mechanism, which does not use the sequence that is to be detected as template. Solely to advance prosecution, and not in acquiescence to the Examiner's rejection, Applicant has amended the claims to more particularly point out and distinguish said features from that of the prior art.

As set out in more detail below, Applicant respectfully submits that the abortive promoter cassette used herein is one of the abortive promoter cassettes of allowed claim 1 of the meanwhile allowed Application No. 10/790,766. Said abortive promoter cassette is comprised of two parts: (a) a self-complementary DNA sequence and an RNA-polymerase binding site and (b) a target-specific linker (which is, in the present case, a nucleic acid). Part (b) is clearly recited by the amendments as introduced to the claims in steps (a) of claim 55 and 56, step (c) of claim 71 and step (b) of claim 113. The target specific linker (part (b)) hybridizes to the sequence that is to be detected, representing the "detection step." After having successfully established a specific interaction between the sequence to be detected and the linker (b) of the abortive promoter cassette by hybridization, the subsequent step lies in the detection of said interaction. One may also

refer in this regard to a readout for the established interaction. In the present case, this readout is done by a mechanism producing reiterative oligonucleotide transcripts, which can be detected. However, Applicant respectfully submits that said readout mechanism itself is completely independent of any target sequence present, but only relies on the presence of part (a) of the abortive promoter cassette, an initiator, an RNA polymerase and a terminator.

In the readout step, the oligonucleotide products are synthesized using a sequence of part (a) of the abortive promoter cassette as template. Said template in part (a) is provided by the abortive promoter cassette and not by the sequence to be detected. This is clearly set out in the specification, e.g., in Figures 19 and 20: Not considering the capture probe depicted therein on the left side for the moment, both figures depict part (a) of the abortive promoter cassette on the right side wherein said part of the cassette is not in contact with the sequence to be detected and, on the 5' side of said cassette, a probe (b) as set out above, which is hybridizing with the sequence to be detected.

Applicant respectfully submits that neither of the prior art cited by the Examiner discloses such a mechanism, i.e. hybridization coupled to abortive transcription wherein the transcriptional step is independent of the target sequence but used as readout of the hybridization. Both prior art documents, Dattagupta and Sasaki *et al.* alone or when combined disclose transcriptional polymerization processes wherein the sequence that is to be detected is used as template (in Dattagupta's case for amplification, in Sasaki's case for sequencing). Applicant respectfully submits that the present invention also clearly differs from prior art cited during the examination proceedings, such as, e.g., US Patent

5,503,979 to Kramer *et al.*, wherein an autocatalytic replication of a sequence, which has been hybridized with the target sequence to be detected, is used as template in the readout step (see e.g., Figure 8 of US 5,503,979). Thus, Kramer *et al.* discloses a detection method using a transcriptional polymerization process wherein a sequence complementary to the sequence that is to be detected is used as template. In Kramer *et al.*, the hybridization probe sequence and the template sequence are identical, whereas, according to the present invention, said sequences are two distinct, separated sequences.

Regarding the abortive promoter cassette, Applicant would like to draw the Examiner's attention to the fact that said abortive promoter cassette was amended such that it exactly reflects the features of an allowed abortive promoter cassette of allowed claim 1 of the meanwhile allowed Application No. 10/790,766 (a continuation of now issued Application No. 09/984,664) wherein the target specific linker is a nucleic acid. Thus, the abortive promoter cassette claimed herein does not comprise a self-complementary DNA sequence as set out in claim 1, (a) (i) and (a) (iii) of allowed Application No. 10/790,766 since the target specific linker used in the present case is a nucleic acid.

According to the above arguments, Applicant respectfully requests that the Examiner reconsider and withdraw the rejection.

The Second 103 Rejection

The Examiner rejected claims 71, 113, 114, 130, 133, 135, 138-140, and 142-148 under 35 U.S.C. § 103(a) as allegedly unpatentable over Dattagupta in view of Sasaki *et al.* and Kang *et al.* (U.S. Pat. No. 6,268,131).

The Examiner applied in the Second Rejection Dattagupta and Sasaki *et al.* as above and further indicated that Dattagupta does not disclose that an immobilized probe is employed in the method. The Examiner asserted that Kang *et al.* disclose a method of sequencing nucleic acid via use of RNA dependent RNA polymerases wherein the transcription of the template is initiated by a promoter sequence. The Examiner further contended that Kang *et al.* teaches an embodiment wherein the primer is immobilized on a solid surface. The Examiner further asserted that it would have been *prima facie* obvious to one of ordinary skill in the art to combine the teachings in the cited art for the purpose of detection/characterizing pathogens in a sample. The Examiner contended that the skilled artisan would have been motivated to combine the cited art to detect pathogens, such as RNA-based pathogens, and would have had a reasonable expectation of success.

Applicant respectfully traverses this rejection and respectfully requests reconsideration. Applicant, respectfully, disagrees with the Examiner's analysis of the cited art.

Applicant refers to the above arguments and submits that the addition of an immobilized probe does not render the invention obvious. It is respectfully submitted that the capture probe as introduced in claims 71 and 114 is an additional probe, which is also hybridizing with the single stranded target polynucleotide that is to be detected. This

concept is depicted in Figures 19 and 20 wherein said capture probe is shown on the left side. In order to clarify that there are two different hybridization regions in the polynucleotide to be detected (one hybridizing to the capture probe and another region [different from the first one] hybridizing to the linker (b) of the abortive promoter cassette) in such embodiments, the phrase "in a different region than the hybridization region mentioned in step (b)" has been introduced in step (c) of currently amended claim 71.

Accordingly, Applicant respectfully requests that the Examiner reconsider and withdraw the rejection.

The Third 103 Rejection

The Examiner rejected claims 131 and 132 under 35 U.S.C. § 103(a) as allegedly unpatentable over Dattagupta in view of Sasaki *et al.* and further in view of Loewy (U.S. Pat. No. 5,914,229).

Applicant respectfully submits that claims 131 and 132 have been canceled.

The Fourth 103 Rejection

The Examiner rejected claims 131 and 132 under 35 U.S.C. § 103(a) as allegedly unpatentable over Dattagupta, Sasaki *et al.*, Kang et al. and further in view of Loewy (U.S. Pat. No. 5,914,229).

Applicant respectfully submits that claims 131 and 132 have been canceled.

Obviousness-type Double Patenting

The Examiner provisionally rejected claims 55-71, 113, 114, 130-135, 138-140, and 142-148 on the ground of nonstatutory obviousness-type double patenting as being allegedly unpatentable over claims 1-22, 32-34, and 44 of copending Appl. No. 10/976,240 Applicant respectfully traverses these rejections.

However, in the interests of advancing prosecution, Applicant submits a terminal disclaimer herewith. Accordingly, it is believed that this rejection can be withdrawn.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicant therefore respectfully requests that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicant believes that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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